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Prescription of beta-blockers in patients with advanced heart failure and preserved left ventricular ejection fraction. Clinical implications and survival (letter)

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Letters to the Editor

Dear Sir,

Increased resting heart rate is inversely associated with life expectancy [1]. Heart rate reduction with beta-blocker treatment has been shown to confer survival benefit in patients with coronary heart disease [2,3]. Daniela Dobre et al. [4] observed that beta-blocker treatment in patients with heart failure and preserved ejection fraction reduce mortality by 43%. They refer to a reduction in heart rate as a possible mechanism of benefit. Baseline average heart rate in their study was quite high, 97.6 beats per minute with a large potential for reduction. The high resting heart rate is associated with poor prognosis and benefit might be expected with heart rate reduction if cardiac output can be maintained. The information on heart rate reduction and survival benefit in heart failure trials is limited. Daniela Dobre and co-workers should provide data on changes in heart rate or blood pressure, which is crucial in understanding the clinical implications of beta-blocker treatment. The information may also be supportive of heart rate reduction as their proposed mode of action. The use of high and low doses of the beta-blockers also warrants some information on the respective changes in resting heart rates among these patients.

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Prescription of beta-blockers in patients with advanced heart failure and preserved left ventricular ejection fraction. Clinical implications and survival

Dear Sir,

We thank Professor Kjekshus for his comments on our paper [1] and agree that reducing heart rate (HR) with beta-blockers might be one of the mechanisms of action by which these drugs work in heart failure (HF) [2]. He correctly points out, that in patients with coronary artery disease, there is an association between the degree of HR lowering by beta-blockers and the magnitude of survival benefit, and wonders whether we can provide data on HR (and blood pressure response) after treatment.

We agree that this data would have been interesting, but unfortunately no follow-up data on HR (and blood pressure) were available in this observational-cohort of patients, and we are therefore not able to comment on the relation between HR lowering and survival in this population.

The evidence for an association between HR lowering and survival benefit is less clear in HF. Although in CIBIS II, the greatest HR reduction was associated with the largest survival benefit [2], in the larger MERIT-HF trial, no such relation could be observed [3]. Moreover, the presence of atrial fibrillation (AF) in patients with HF may also play a role in this respect. Recently, it was shown that while patients with AF had a similar reduction in HR as those with sinus rhythm at baseline, there was no effect on survival in the AF group [4], and a similar finding was reported in the CIBIS-II trial [2]. Interestingly, as many as 45% of patients had AF in our observational study [1] and it would have been interesting to compare the effects on HR reduction and survival in both patients with AF and in those with sinus rhythm.

Another factor in both survival and reduction of HR in HF is of course the dose of beta-blocker used. In our study, we found that higher doses of beta-blockers exerted a higher benefit than lower doses [1]. Similarly, we recently showed in a post-hoc analysis from the SENIORS study that higher maintenance doses of nebivolol achieved a higher benefit than lower doses, while patients unable to tolerate any dose had the worst prognosis [5]. Only one randomised trial has so far prospectively examined the effect of beta-blocker dose in HF patients, and this MOCHA study [6] showed a dose-related improvement in ejection fraction and survival while no dose-related reduction in HR and blood pressure was associated with the clinical outcome.

In summary, although we generally agree with Professor Kjekshus about HR reduction and survival, this relation is less pronounced in HF, while AF and dose also play a role. More prospective data are needed on this subject.

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RAS blockers: Does sex matter? Re: Sex differences in the effectiveness of ARB and ACEI in patients with congestive heart failure — A population study: Marie Hudson et al. *European Journal of Heart Failure* 9 (2007) 602–609

The retrospective analysis by Hudson et al. [1] suggests that the global mortality of male patients discharged post hospitalization for CHF with a prescription for ARB was no

different than for an ACEI, with a survival advantage for females prescribed ARB. Randomized prospective trials would suggest otherwise.

A meta-analysis of trials that randomized ARB vs. ACEI (ELITE I, ELITE II, OPTIMAAL, VALIANT, DETAIL; $n=19,419$, 99% with CHF) [2] found a greater global mortality with ARB than ACEI (OR 1.06 .99–1.14, $p=.1$). The majority of patients were post an acute MI. In OPTIMAAL[3] ($n=5477$), cardiovascular mortality was significantly increased with losartan as compared to captopril (OR 1.17 CI 1.01–1.34) despite a mean follow up of just 2.7 years. The mortality rate in VALIANT ($n=9818$) [4] was not statistically different for valsartan and captopril (19.9% vs.19.5% respectively). Although VALIANT was event driven, one could argue that the follow-up of 24.7 months was just simply too short to differentiate drug efficacy considering the cardiovascular benefits of ACEI in SAVE and SOLVD, both placebo controlled trials, took 3.5 years to achieved significance. VALIANT was a negative “superiority” trial and as such, the “apparent” absence of a difference in mortality does not rule out that a clinically important difference exists, nor can it prove statistical equivalence.

In Hudson’s [1] retrospective analysis, 13% of patients were prescribed ARB over ACEI despite guidelines recommending otherwise. Bias on the part of physicians is the likely explanation and statistical models can not adjust for this. Follow-up of only 2–3 years with relatively small numbers prescribed ARB ($n=2587$) as compared to ACEI ($n=17,111$) may accentuate any bias and contribute to conclusions that are erroneous. This may account for the apparent survival advantage in females with ARB, but not in males, with the inference being that ACEI have reduced efficacy in females. This appears not to be so, as a meta-analysis of placebo controlled CHF trials with ACEI demonstrated a similar survival advantage in women ($n=2373$, HR 0.80, 95% CI 0.76–.85) [5] as in men.

ACEI are well established as the preferential therapy over ARB for CHF, regardless of gender. A multiplicity of meta-analyses supports a similar conclusion for all “high risk patients”. In a meta-analysis of 150,943 patients[2], ACEI reduced the risk of MI by 14% ($p<.00001$) and CV death by 12% ($p<.0005$). Four separate meta-analyses of ARB ($n=56,254–68,711$)[2,6–8] failed to demonstrate *any* reduction in either MI or CV death. Two meta-regression analyses ($n=136,838$ and $179,122$) [9,10] suggest that the benefits of ACEI on the combined endpoint of MI and CV death was significantly greater than could be predicted by blood pressure lowering alone (9% and 12% respectively). “Blood pressure independent” effects are unique to ACEI [9,10] and are not evident with ARB [9].

A retrospective analysis can at best generate plausible hypotheses — with the emphasis on the word “plausible”. Further division into sub-groups adds little, as one sub-group will tend to do better, and the other worse, than the overall